



# Idiopathic CD4 T-Lymphocytopenia in a Patient with Disseminated Tuberculosis

## Yaygın Tüberkülozlu Bir Hastada İdiyopatik CD4 T-Lenfositopenisi

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### Abstract

We present a 26-year-old male patient with a negative serological testing for human immunodeficiency virus, miliary tuberculosis with significant T-lymphocytopenia, multifocal skeletal involvements including the vertebrae and wrist, and in addition, right gluteal and bilateral iliopsoas abscesses. *Mycobacterium tuberculosis* was isolated from drainage fluid of abscesses and bronchial lavage cultures. The CD4 T-lymphocyte ratio, which had previously been determined to be 13% with flow cytometric analysis of peripheral blood, remained at low levels throughout the treatment period (14% to 20%). Although there was a slight increase in CD4 T-lymphocyte percentages (19% and 22%, respectively), and absolute CD4 T-lymphocyte counts (359/mm<sup>3</sup> and 364/mm<sup>3</sup>, respectively) studied on the third and ninth months after discontinuation of treatment, it remained at low levels. The researchers observed rapid recovery in this case that underwent both percutaneous drainage, and chemotherapy treatment failure or relapse has not been observed in such a patient with immunodeficiency.

**Key words:** *Gluteal abscess, iliopsoas abscess, lymphocytopenia, miliary tuberculosis, skeletal tuberculosis.*

### Özet

Yirmi altı yaşında serolojik olarak insan immün yetmezlik virusu negatif olan, belirgin T-lenfopeni ile miliyer tüberkülozu, vertebra ve elbileğini içeren birden çok odakta iskelet tutulumları ve ek olarak, sağ gluteal ve bilateral iliopsoas abseleri olan bir erkek hasta sunuldu. Abselerden elde edilen drenaj materyali ve bronş lavajı kültürlerinden *Mycobacterium tuberculosis* izole edildi. Başlangıçta, periferik kanda akım-sitometrik analiz ile %13 olarak tespit edilen CD4 T-lenfosit oranı, tedavi periyodu boyunca düşük seviyelerde kaldı (%14 ila %20). Her ne kadar tedavi tamamlandıktan sonra 3üncü ve 9 uncu aylarda bakılan CD4 T lenfosit oranları (sırasıyla %19 ve %22) ve mutlak değerleri (359/mm<sup>3</sup> ve 364/mm<sup>3</sup>) hafif bir artış gösterse de, düşük seviyede kalmıştır. Hem kemoterapi hem de abseler için perkütan drenaj uygulanan böyle bir immünyetmezlikli hastada hızlı bir düzelmeye olduğu ve relaps gelişmediği gözlemlendi.

**Anahtar Sözcükler:** *Gluteal abse, iliopsoas abse, lenfositopeni, miliyer tüberküloz, iskelet tüberkülozu.*

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Submitted (Başvuru tarihi): 07.06.2013 Accepted (Kabul tarihi): 31.07.2013

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One to three percent of all tuberculosis cases have skeletal involvement, but the involvement of the wrist and sacral vertebra is rare (1). Miliary tuberculosis develops due to intense hematogenous spread of tuberculosis bacillus during or a long time after primary infection. The degree of tuberculosis bacillemia and immune competence of the host are critical factors in determining the outcome of this spread. Estimating the amount of CD4 cells is key in assessing the health of the immune system. Low amounts are typically seen in HIV infection. Individuals with a CD4 cell number of  $<200/\text{mm}^3$  and a ratio of  $<14\%$  are strongly recommended to be evaluated for HIV infection (2). Idiopathic CD4 T-lymphocytopenia (ICL) is a rare immunodeficiency condition affecting 0.0002% of the adults. This condition is characterized by a CD4 T-lymphocyte count of  $<300/\text{mm}^3$  or a ratio of the number of CD4 T-lymphocytes to the total number of T cells  $<20\%$ . It was first defined by the US Center for Disease Control and Prevention (CDC) in 1992 (3). It has been suggested that HIV infection that can give rise to T-lymphocytopenia or another defined immunodeficiency condition or cytotoxic drug use should be excluded (4).

## CASE

A 26-year-old male patient, who presented to another center with complaints of sweating, loss of appetite, pain in the right leg, and difficulty in walking, and whose chest X-ray and computed tomography examinations were compatible with miliary tuberculosis, was referred to our clinic. On admission, he did not have complaints of cough, expectoration, or shortness of breath or hemoptysis. The patient with a 10 pack-/year smoking history did not have a history of contact with tuberculosis or a risk factor such as HIV positivity. The patient did not have any remarkable medical history. He is employed as a clothing salesman. The patient, with a history of pain and swelling of the left wrist after being struck by ball 3 years ago, underwent puncture and a yellow-colored fluid was obtained. The patient's complaints of limitation of movement in this region and a yellow-colored drainage continued.

A physical examination performed on admission revealed no significant findings. His body temperature was  $36.7^\circ\text{C}$ ; blood pressure was 90/50 mmHg. Auscultation of the chest revealed no abnormal sounds. No superficial lymph nodes were palpable. Left wrist motions were restricted and painful; two scar lesions were presented on the volar site. Through the follow-up, the patient had night sweats, but did not have any fever.

The laboratory findings were as follows: sedimentation rate: 72 mm/h; leukocytes:  $9950/\text{mm}^3$ ; neutrophils: 78.6%, lymphocytes: 16 %; hemoglobin: 11.9 g/dL; platelets:  $408000/\text{mm}^3$ ; sensitive CRP: 32.9 mg/l; SGOT: 19 U/L; SGPT: 17 U/L; GGT: 21 U/L; LDH: 139 U/L; glucose: 96 mg/dL; creatinine: 0.8 mg/dL; urea: 19 mg/dL; and albumin: 3.5 g/dL. Alpha-fetoprotein, carcinoembryonic antigen, Ca15.3, Ca19.9, and Ca125 were negative; HBs Ag, anti HBC, anti-HCV, and anti-HB were also negative. Tube agglutination tests for brucellosis and salmonella were negative; HIV tests were also negative. Antinuclear antibody and anti-dsDNA by ELISA and anti-neutrophil cytoplasmic antibody were negative; rheumatoid factor (RF) was 20 IU/mL. Serum IgG and IgA levels were higher than normal [IgG: 23.4g/dL (N: 7.51 g/dL-15.6 g/dL), IgA: 5.59 g/dL (N: 0.82 g/dL-4.53 g/dL)] and IgE and IgM levels were normal. These values were interpreted as an inflammation secondary to chronic infection. The CD4/CD8 ratio, studied simultaneously in serum, and bronchoalveolar lavage (BAL) were 0.4 and 2.4, respectively. Flow-cytometric analysis of the patient is shown Table 1.

The tuberculin skin test (PPD) showed an induration of 10 mm and the patient had a history of BCG vaccination. Thoracic computed tomography (CT) examination revealed diffuse miliary micronodular lesions and a cavitary nodular lesion of 8x12 mm in size at the apex of the right upper lobe (Fig 1). Abdominal magnetic resonance imaging (MRI) revealed discitis of the L5-S1 intervertebral discs and intense inflammatory signal changes in the bones adjacent to the joints (Fig 2), and abscess foci extending inferiorly from this level and extending from the posterior side of the iliopsoas muscle to the pelvis at the right side and extending from the medial side of the iliopsoas muscle to the pelvis at the left side. Another abscess extended from the presacral area in the right gluteus muscle through the sciatic foramen, and its gluteal component from the sciatic foramen, reached approximately 10x4.5 cm in size. MR imaging of the left hand revealed synovitis and diffuse edema of the bones. Bronchoscopic findings were normal, and transbronchial biopsy revealed no pathology. A direct smear of bronchial lavage showed no acid-resistant bacteria (ARB), but *M. tuberculosis* was isolated from lavage culture. Percutaneous catheters were placed in the three abscesses in the abdomen. A total of 275 cc of abscess material was eliminated over 23 days. Direct smears of abscess drainage material were positive for ARB. *M. tuberculosis* was isolated from the drainage

**Table 1.** Description of the laboratory findings of the patient.

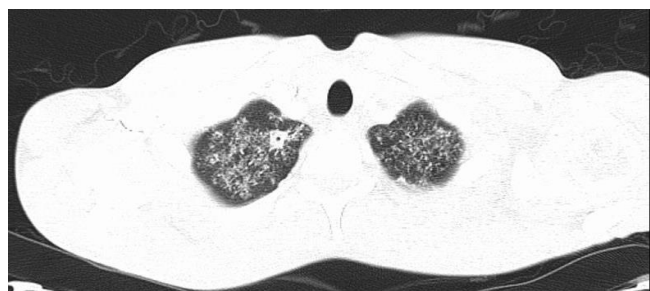
	At admission	During treatment	3 month After treatment	Reference Values ‡
Total lymphocytes (/mm <sup>3</sup> )	1590	1990	1520	1700-5700
T lymphocytes (CD3+) (%)	50	53	56	58-82
(Count/mm <sup>3</sup> )	795	1054	851	1000-4100
T helper cells (CD4+) (%)	13	14	19	28-51
(Count/mm <sup>3</sup> )	206	278	288	600-2400
Cytotoxic T cells (CD8+) (%)	26	28	33	16-42
(Count/mm <sup>3</sup> )	413	557	501	400-1500
Natural killer cells (%)	19	23	5	8-30
(CD16+56+) (Count/mm <sup>3</sup> )	302	365		(200-1000)
B lymphocytes (CD19+) (%)	22	20	10	10-28
(Count/mm <sup>3</sup> )	350	318		200-1400
IgG (mg/dl)	2340		1680	751-1560
IgA (mg/dl)	559		362	82-453
IgM (mg/dl)	59			46-304
IgE (IU/ml)	296		108	0-165
Tuberculin test (mm)	10			5-10
In vitro PHA * (%)	68			65.8 ± 9.2
CD25 expression on CD4+ T lymphocytes † (%)	3	15		12-30
Phagocytosis	2.48	2.08		>1.5
Chemotaxis	3.42	1.77		>1.5
Respiratory burst activity	56.8	9.65		>1.5

\* In vitro lymphocyte stimulation using phytohemagglutinin, values refer to the percentages of the blastic transformation of lymphocytes,

† Flowcytometric values of CD25 expression on CD4+ T lymphocytes after lymphocyte stimulation using PHA,

‡ Normal values in age-matched Turkish subjects.

material culture and was sensitive to all first-line tuberculosis drugs. Antituberculous treatment comprised of isoniazid, rifampicin, pyrazinamide and ethambutol was commenced. Chest CT, abdominal MRI and MR imaging of the wrist, taken in the ninth month of the treatment period showed significant improvement and treatment continued for 12 months. The subsequent nine-month follow-up period showed no recurrence. The CD4 T-lymphocyte ratio, which was previously determined to be 13% with flow cytometric analysis of peripheral blood, remained at low levels throughout the treatment period. In-vitro lymphocyte functions re-evaluated during and after the treatment were normal. Although there was a slight increase in CD4 T-lymphocyte percentages and absolute CD4 T-lymphocyte counts studied on the third and ninth months after discontinuation of the treatment, they remained at low levels (Table 1). However, the patient continues to be followed in terms of lymphocyte counts and opportunistic infections.



**Figure 1:** Thoracic computed tomography examination revealed diffuse miliary micronodular lesions and a cavitary nodular lesion which was 8x12 mm in size at the apex of the right upper lobe.

## DISCUSSION

There are many issues in the literature focusing on the cases of miliary tuberculosis associated with leukemia, lymphoma, renal failure, dialysis, and transplantation (1). Although the present case was not found to have any of these diseases, the patient had pulmonary involvement, multifocal bone involvement, and three foci of abdominal abscesses. The researchers believe that the patient might primarily have an immunodeficiency disorder. The patient had a negative serological testing for HIV. Flow-cytometric analysis revealed a decrease in the ratio and absolute numbers of total and helper T-lymphocytes (CD4). Therefore, the patient was diagnosed with idiopathic CD4+ lymphocytopenia (ICL). As in the current case, ICLs have been reported to occur with opportunistic infections (OI) (*Cryptococcus*, *Mycobacteriosis*, *Human papilloma virus*, and *herpes zoster*, in particular) (2). In a retrospective study, CD4 T-lymphocyte count was found

to be  $<300$  cells/mm<sup>3</sup> in 9.6% of 115 HIV-negative hospitalized patients with tuberculosis, whereas this rate was 4.2% in 312 outpatients with tuberculosis and 0.4% in 263 healthy women who have recently given birth. (5). In addition, CD4 lymphocytopenia has been associated with extrapulmonary tuberculosis and more severe forms of mycobacterial infections (6). In the current patient, diffuse extrapulmonary involvement was compatible with this information. Clinical patterns of skeletal tuberculosis are spondylitis, osteomyelitis, peripheral joint infections and soft tissue abscesses. Fifty to sixty percent of skeletal involvements are vertebral involvement (7). Vertebral lesions have been reported to develop secondary to a demonstrable primary focus in any part of the body and be involved mainly during hematogenous spread. The most frequently affected region has been reported to be the thoracolumbar region; the sacral involvement seen in the current patient was reported to be rarely seen (8). The second most common site of involvement is the joints, where the involvement may occur via direct invasion from the site of tuberculous osteomyelitis or via hematogenous spread. This disease is typically a monoarticular disease (90%). Any joint may be involved, but the involvement of the wrist is extremely rare ( $<1\%$ ) (1). The diagnosis of tuberculous arthritis is confirmed by the histological and culture examination of synovial fluid and tissue (9). Specific diagnosis could not be achieved with histopathological and bacteriological examination of our patient. However, the regression of the lesion after the initiation of tuberculosis treatment, improvement in MRI findings taken after four and nine months, and disappearance of wrist pain and movement limitation confirmed the diagnosis of tuberculous arthritis. The iliopsoas muscle extends from the T12 vertebra up to the lesser femoral trochanter. It is closely associated with retroperitoneal organs, the pelvis, and thighs. Vertebral infections can spread to the pelvis and thigh through the iliopsoas compartment (1). MR images of the current case showed a spread to the pelvis through the right iliopsoas compartment and an abscess foci extending from the presacral area to the gluteal region through the sciatic foramen. Psoas abscesses are relatively rare clinical entities, with an incidence of approximately 12 cases per year in the medical literature, and may be caused by different etiological agents (*Staphylococcus aureus*, *proteus*, *Pasteurella multocida*, *bacteroides*, *clostridium*, *Yersinia enterocolitica*, *klebsiella*, etc...) of which one can be *Mycobacterium tuberculosis* (10). High fever has been reported to be a frequent sign in miliary tuberculosis; however, in the current case, the

patient had no fever, a possible cause of which might have been a decline in CD4 T-lymphocytes count.



**Figure 2:** Abdominal magnetic resonance imaging (MRI) findings: Discitis of L5-S1 intervertebral discs and intense inflammatory signal changes in bones adjacent to the joints.

In many patients with disseminated mycobacterial infection, an improvement in the CD4 T-lymphocyte count with 4-8 weeks of antituberculous therapy, which suggests that CD4 lymphopenia is an outcome of the infections, rather than the cause (11). In this case, the number and ratio of T-lymphocytes were re-evaluated three months and nine months after discontinuation of the treatment in order to conclude that the lower number and ratio of T-lymphocytes at baseline were due to a temporary immune suppression related to tuberculosis infection or due to an underlying permanent immunodeficiency, and the ratio and absolute numbers of CD4+ T lymphocytes were still lower than normal. However, lymphocyte responses in the culture media and CD25 expression responses to lymphoblastic transformation and stimuli were found to be normal. The patient is being followed in terms of continuing low levels of CD4 T-lymphocytes and also opportunistic infections. There was no recurrence or another opportunistic infection in the one year period after the discontinuation of antituberculosis treatment.

The researchers would like to emphasize the importance of CD4 T-lymphocyte depletion associated with dissemi-

nate tuberculosis in persons without HIV infection. Pre-treatment immune system abnormalities did not create an additional challenge in the treatment of tuberculosis. The researchers observed a rapid recovery the patient that underwent both percutaneous drainage and chemotherapy.

## CONFLICTS OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

Concept - A.Z., Ş.Y., İ.R.; Planning and Design - A.Z., Ş.Y., İ.R.; Supervision - A.Z., Ş.Y., İ.R.; Data Collection and/or Processing - İ.R.; Analysis and/or Interpretation - A.Z.; Literature Review - Ş.Y.; Critical Review - A.Z., Ş.Y., İ.R.

## YAZAR KATKILARI

Fikir - A.Z., Ş.Y., İ.R.; Tasarım ve Dizayn - A.Z., Ş.Y., İ.R.; Denetleme - A.Z., Ş.Y., İ.R.; Veri Toplama ve/veya İşleme - İ.R.; Analiz ve/veya Yorum - A.Z.; Literatür Taraması - Ş.Y.; Eleştirel İnceleme - A.Z., Ş.Y., İ.R.

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